REMARKS

Applicants respectfully request entry of the current amendments to the claims. Applicants believe that the present amendments place all of the claims in condition for allowance, or in a better condition for appeal.

In the Office Action dated August 14, 2003, the Examiner indicated that she had withdrawn the previous Requirement for Restriction and, consequently, claims 1-97 are now under examination. By virtue of this response, Claims 2, 22, and 42 have been amended, Claims 65-97 have been canceled, and Claim 98 is newly presented.

Further, the Examiner acknowledged receipt of Information Disclosure Statements filed September 3, 2002, November 6, 2002 and December 10, 2002 as Papers 4, 5 and 6 respectively, and stated that each had been reviewed to the extent references were provided or readily available. Specifically, applicants note that the Examiner did not initial all the references presented in Paper 4, presumably due to lack of availability of the references. Applicants will further review the list for completeness and will rectify the references, to the extent necessary, by way of a separate communication.

Amendments

The specification has been amended to correct an obvious typographical error in the citation of the priority documents and to update the listing to include the previously unknown provisional application serial number. These reference numbers can be verified with reference to the filing receipt mailed 4/2/2002.

Claims 2, 22, and 42 have been amended to bring out the feature of the invention that the non-alpha tocopherol metabolites of the invention are natural metabolites of beta-tocopherol, gamma-tocopherol or delta-tocopherol. Support for this aspect of the invention can be found, for example, at page 23, lines 5-14 thereof and in the Drawings at Figure 3.

Claims 41 and 42 have been amended to bring out the feature that the method of the invention is effective to reduce tissue or cell death associated with non-cardiovascular tissue

ischemia. Support for this aspect of the invention can be found, for example, at page 13, lines 14-21 of the specification.

Claims 65-97 are canceled by this amendment.

New claim 98 is added to bring out the feature that a specific gamma tocopherol metabolite is gamma-CEHC. Support for this feature of the invention may be found, for example, at page 22, lines 7-14 of the specification.

The foregoing amendments and/or cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. With respect to all amendments and canceled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in a future continuation and/or divisional application. No new matter has been added.

Rejections under 35 U.S.C. §112, second paragraph

Claims 65-69, 76-81, 85, and 87 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. By this amendment, Claims 65-69, 76-81, 85, and 87 have canceled.

In view of the foregoing amendments to the claims, applicants believe that pending claims are in compliance with 35 U.S.C §112, second paragraph. Withdrawal of the rejection under this section is therefore respectfully requested.

Rejections under 35 U.S.C. §112, first paragraph

Claims 3-5, 7, 8, 24-32, 39-41 and 48-50 were rejected under 35 U.S.C. § 112, first paragraph on the grounds that the specification, while being enabling for the administration of

gamma, beta, delta tocopherols and the metabolite gamma-CEHC to treat ischemia, does not provide enablement for any metabolite of gamma, delta or beta tocopherol, or any flavonoid in the treatment of ischemic conditions. It is the Examiner's position that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use of the invention commensurate in scope with these claims.

Applicants believe that the Examiner may have mis-numbered the claims in question under this section, since the claims listed above do not all include metabolite and/or flavonoid language. It is believed that the Examiner wished to refer to Claims 2, 11-13 (reciting beta-tocopherol metabolites), 22, 31-33 (reciting delta-tocopherol metabolites), 42, 53-57 (reciting gamma-tocopherol metabolites), and 65-97 (reciting flavonoids). Claims 65-97 are canceled by virtue of the present amendment; accordingly applicants will direct their remarks to the Examiner's rejection of Claims 2, 11-13, 22, 31-33, 42, and 53-57, all of which recite tocopherol-metabolites.

The test of enablement is whether the applicants have taught how to make and use the invention as claimed.

> As a matter of Patent Office practice... a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of §112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971).

Further the court in *Marzocchi* has stated, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." MPEP 2164.04; In re Marzocchi, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

By the present amendment, independent Claims 2, 22 and 42 have been amended to bring out the feature that anti-ischemic non-alpha tocopherol metabolites are natural metabolites of beta-,

delta- or gamma-tocopherol. Applicants submit that such metabolites and how to make them are well known in the art. See, for example, their statement made in the specification:

> "It is well known that gamma-tocopherol is metabolized *in vivo* to form, for example, gamma-CEHC and gamma-CEBC, among other metabolites. In humans, this metabolite is thought to be the result of sequential oxidation of its phytyl sidechain by enzymes that catalyze omega and beta oxidation." (specification at page 59, lines 17-21)

In addition, applicants have described other tocopherol metabolites, for example at page 22, line 23 to page 23, line 14, of the specification. Further detail is provided, for example, at pages 41-53 of the specification and in the Drawings at Figure 3, where applicants have provided further, detailed structures of the types of metabolites that are natural by-products of mammalian metabolism of the subject tocopherols. Such compounds are either generally commercially available, or can be produced synthetically by commonly known methods, or can even be isolated from natural sources (see, for example U.S. Patents 6,150,402, 6,083,982, 6,048,891 and 6,242,479, which were specifically incorporated by reference into the instant application).

Further support for breath of the applicants' claimed invention is provided by way of a Declaration by Dr. Sekhar Boddupalli, submitted herewith in accordance with 35 U.S.C. §1.132. In his statement, Dr. Boddupalli describes the activity of various natural tocopherol metabolites in certain experimental models of cell and tissue ischemia.

Furthermore, the applicants have described in detail in the specification how to formulate such compounds into a variety of forms suitable for administration to mammalian subjects, and appropriate dosage schedules for such administration (as described, for example, at page 14, line 1 to page 18, line 20; page 33, line 12 to page 37, line 18; page 68, line 4 to page 69, line 27; and page 71, line 27 to page 78, line 24 of the specification). Further, the applicants have described in detail how use such formulations to ameliorate the symptoms of certain tissue ischemic conditions, as described, for example at pages page 61, line14, to page 67, line 28 of the specification.

Accordingly, applicants submit that they have provided sufficient guidance to enable persons skilled in the art to make and use the invention as presently claimed. The Examiner has not provided any documentation or evidence as to why it doubts the truth or accuracy of applicants' assertions in this regard.

In view of the foregoing amendments and remarks, applicants respectfully submit that the instant specification complies with the enablement requirements of 35 U.S.C. §112, first paragraph. Accordingly, withdrawal of the objections and rejections thereunder are respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Claims 41-63 stand rejected as unpatentable over Wechter, W.J. (WO 00/35444; "Wechter"). It is the Examiner's position that Wechter's teaching the use gamma-tocopherol and its metabolite LLU-α in the treatment of ineffective renal perfusion would render obvious the use of gamma tocopherol or a derivative of gamma tocopherol to treat renal ischemia.

In essence, the Examiner's position is that the applicant's claimed invention would be *prima facie* obvious over the Wechter publication alone. The Examiner cites Wechter's teaching of the use of gamma tocopherol and the metabolite LLU-α for use ineffective renal perfusion, which the Examiner characterizes as a noncardiovascular tissue ischemic condition. The Examiner further asserts that one skilled in the nephrology art would have been motivated to administer gamma-tocopherol or a derivative of gamma tocopherol to treat renal ischemia, in view of Wechter.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (MPEP 2143).

Independent claims 41 and 42 have been amended to bring out the feature that the method of the claimed invention is directed at reducing cell or tissue death associated with non-cardiovascular tissue ischemic conditions in mammalian subjects, by administering an effective amount of a gamma-tocopherol or gamma-tocopherol metabolite-enriched composition.

The Wechter reference does not show or suggest that gamma tocopherol or gamma-tocopherol metabolites are useful in reducing cell or tissue death associated with non-cardiovascular tissue ischemic conditions. Rather, Wechter provides data showing increase in sodium excretion (natriuresis), when the gamma tocopherol metabolite LLU-α or LLU-γ was infused into rats (Wechter, WO 00/35444, Example 2, pages 27-29). Such a natriuretic effect, while associated with kidney perfusion and function, does not imply or suggest that the compounds are useful in reducing cell or tissue death associated with tissue ischemia. Nor would there be any motivation to use the compounds in such a capacity or a reasonable expectation of success of such an outcome, absent the teachings of the applicants' disclosure. Accordingly, the applicants' claimed invention cannot be said to be obvious in view of Wechter.

In view of the foregoing, withdrawal of the rejections under 35 U.S.C. §103(a) is respectfully requested.

Rejections under 35 U.S.C. § 102(e)

Claims 1-7, 14-27, 34-43 and 58-97 stand rejected under 35 U.S.C. §102(e) as being anticipated by Brown et al., U.S. Patent 6,528,042 ("Brown"). Claims 65-97 stand canceled by the present amendment. Therefore, the remarks that follow are directed to the pending claims.

In order to qualify as a reference under 35 U.S.C. §102(e), the subject patent must be granted on an application for patent by another filed in the United States before the invention by the applicant for patent.

Without arguing the merits of the Examiner's rejection under this section, Applicants respectfully draw the attention of the Examiner to the fact that the inventive entity of the Brown reference is: Lesley A. Brown and Guy Miller of Galileo Laboratories, Inc. The inventive entity of the instant application is: Lesley A. Brown, Guy Miller, Ughetta del Balzo, Stephen Flaim, Sekhar Boddupalli, Bing Wang of Galileo Laboratories, Inc. (which has subsequently changed its name to Galileo Pharmaceuticals, Inc.). Since the inventive entity of the earlier application overlaps with and has fewer than the inventive entity of the instant application, it cannot be said to be "by another" within the definition of 35 U.S.C. §102(e). A Declaration under 37 C.F.R. §1.132 by common

inventor Guy Miller stating that any disclosed but unclaimed material in the Brown '042 patent is attributable to him and to his co-inventor, Lesley A. Brown.

In addition, even if the Brown reference were considered to be a proper reference under 35 U.S.C. §102(e), applicants respectfully submit that the Brown reference does not anticipate the subject matter of Claims 1-7, 14-27 and 34-43, and 58-64, now pending in the instant application.

The Brown '042 patent describes the use of certain flavonoids in combination with a synergist compound for ameliorating disruption of energy metabolism secondary to stress. Nowhere does Brown show or suggest that a delta-, beta-, gamma-tocopherol or metabolite thereof is effective to reduce treating and/or ameliorating the symptoms of a tissue ischemic condition in a mammalian subject. While Brown describes certain tocopherols as possible synergists, Brown actually teaches against the concept of tocopherols alone as therapeutic agents in this regard. (See, for example, column 49, lines 55 to 65, where gamma-tocopherol was stated to have no cytoprotective activity by itself).

Accordingly, applicants respectfully request that the Examiner withdraw the rejection of the claims under 35 U.S.C. §102(e).

Rejections under Judicially-created Prohibition against Double-Patenting

Claims 1-64 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over co-owned, co-pending U.S. Patent Application 10/020,450. The Examiner states that this rejection is provisional, since the conflicting claims have not yet been patented.

Applicants respectfully request that this rejection be held in abeyance until such time as the claims in the instant case are found to be in condition for allowance, at which time it should be considered whether the allowed claims are, in fact, in conflict with the claims of USSN 10/020,450.

CONCLUSION

Applicants respectfully submit that all issues raised in the Office action have been properly addressed in this response and that the claims pending in the application are now in condition for allowance. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, she is encouraged to contact the undersigned at the telephone number provided below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-2859** referencing docket no. 104732001200. However, the Assistant Commissioner is not authorized to charge the cost of the Issue Fee to the Deposit Account.

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Respectfully submitted,

By _____

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